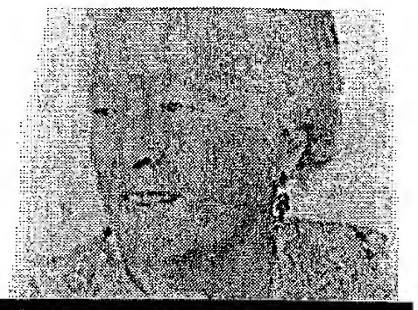
800-438-4380

# A D E A R
# Alzheimer's Disease Education & Referral Center

A Service of the National Institute on Aging





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## General Information

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**Other questions?**
Call **1-800-438-4380** or e-mail our Information Specialists.

**What is Alzheimer's disease (AD)?**

Alzheimer's disease (AD) is the most common form of dementia (a brain disorder that seriously affects a person's ability to carry out daily activities) among older people. It involves the parts of the brain that control thought, memory, and language. Every day scientists learn more, but right now the causes of AD are still unknown, and there is no cure.

AD is named after Dr. Alois Alzheimer, a German doctor. In 1906, Dr. Alzheimer noticed changes in the brain tissue of a woman who had died of an unusual mental illness. He found abnormal clumps (now called amyloid plaques) and tangled bundles of fibers (now called neurofibrillary tangles). Today, these plaques and tangles in the brain are considered hallmarks of AD.

Scientists also have found other brain changes in people with AD. There is a loss of nerve cells in areas of the brain that are vital to memory and other mental abilities. There also are lower levels of chemicals in the brain that carry complex messages back and forth between nerve cells. AD may disrupt normal thinking and memory by blocking these

messages between nerve cells.

**View Video: Alzheimer's Disease Process** (2 minutes, captioned)
You will need free RealPlayer to view this video. Download free RealPlayer.

- Alzheimer's Disease Process - Broadband (DSL)
- Alzheimer's Disease Process - Modem (56K)

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**How many Americans have AD?**
Scientists think that up to 4 million Americans suffer from AD. The disease usually begins after age 60, and risk goes up with age. While younger people also may get AD, it is much less common. About 3 percent of men and women ages 65 to 74 have AD, and nearly half of those age 85 and older may have the disease. It is important to note, however, that AD is *not* a normal part of aging.

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**How long can a person live with AD?**
AD is a slow disease, starting with mild memory problems and ending with severe brain damage. The course the disease takes and how fast changes occur vary from person to person. On average, AD patients live from 8 to 10 years after they are diagnosed, though the disease can last for as many as 20 years.

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**What is Dementia?**
The term "dementia" describes a group of symptoms that are caused by changes in brain function. Dementia symptoms may include asking the same questions repeatedly; becoming lost in familiar places; being unable to follow directions; getting disoriented about time, people, and places; and neglecting personal safety, hygiene, and nutrition. People with dementia lose their abilities at different rates.

Dementia is caused by many conditions. Some conditions that cause dementia can be reversed, and others cannot. The two most common forms of dementia in older people are Alzheimer's disease and multi-infarct dementia (sometimes called vascular dementia). These types of dementia are irreversible, which means they cannot be cured.

Reversible conditions with symptoms of dementia can be caused by a high fever, dehydration, vitamin deficiency and poor nutrition, bad reactions to medicines, problems with the thyroid gland, or a minor head injury. Medical conditions like these can be serious and should be treated by a doctor as soon as possible.

Sometimes older people have emotional problems that can be mistaken for dementia. Feeling sad, lonely, worried, or bored may be more

common for older people facing retirement or coping with the death of a spouse, relative, or friend. Adapting to these changes leaves some people feeling confused or forgetful. Emotional problems can be eased by supportive friends and family, or by professional help from a doctor or counselor.

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**What is Multi-Infarct Dementia (MID)?**
In multi-infarct dementia, a series of small strokes or changes in the brain's blood supply may result in the death of brain tissue. The location in the brain where the small strokes occur determines the seriousness of the problem and the symptoms that arise. Symptoms that begin suddenly may be a sign of this kind of dementia. People with multi-infarct dementia are likely to show signs of improvement or remain stable for long periods of time, then quickly develop new symptoms if more strokes occur. In many people with multi-infarct dementia, high blood pressure is to blame. One of the most important reasons for controlling high blood pressure is to prevent strokes.

**More information on other types of dementia:**
- Multi-Infarct Dementia (Vascular Dementia)
- Dementia with Lewy Bodies
- Frontotemporal Dementia

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**What is Mild Cognitive Impairment (MCI)?**
Recently, scientists have focused on a type of memory change called mild cognitive impairment (MCI). MCI is different from both AD and normal age-related memory change. People with MCI have ongoing memory problems but do not have other losses like confusion, attention problems, and difficulty with language. Scientists funded by the National Institute on Aging (NIA) are conducting the Memory Impairment Study to learn whether early diagnosis and treatment of MCI might prevent or slow further memory loss, including the development of AD.

## Other questions?
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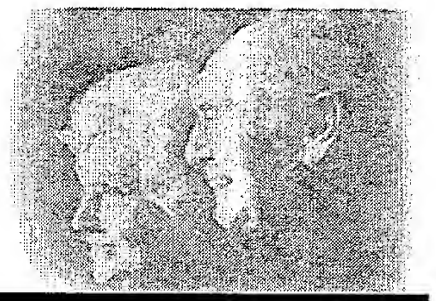





# ALZHEIMER'S DISEASE
# Unraveling the Mystery

## The Search for Causes

One of the most important parts of unraveling the AD mystery is finding out what causes the disease. What makes the disease process begin in the first place? What makes it worse over time? Why does the number of people with the disease increase with age? Why does one person develop it and another remain healthy?

Some diseases, like measles or pneumonia, have clear-cut causes. They can be prevented with vaccines or cured with antibiotics. Others, such as diabetes or arthritis, develop when genetic, lifestyle, and environmental factors work together to cause a disease process to start. The importance of each one of these factors may be different for each individual.

AD fits into this second group of diseases. We don't yet fully understand what causes AD, but we know it develops because of a complex series of events that take place in the brain over a long period of time. Many studies are exploring the factors involved in the cause and development of AD.

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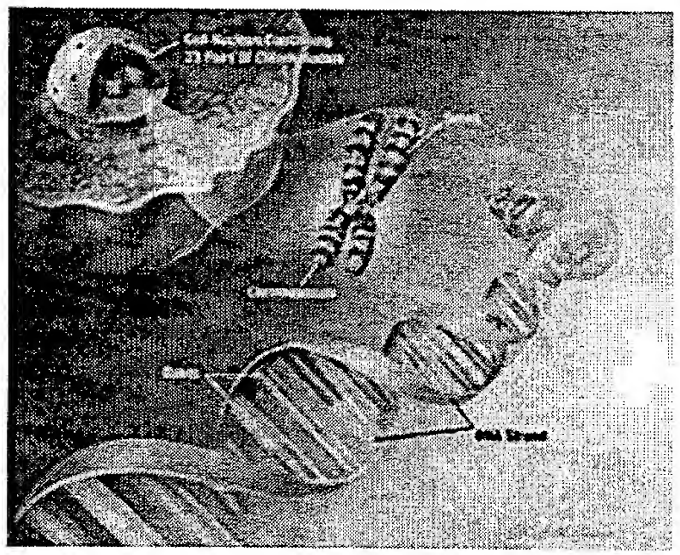
**Genetic Factors at Work in AD**

In the last few years, painstaking detective work by scientists has paid off in discoveries of genetic links to the two main types of AD. One type is the more rare, early-onset Alzheimer's disease. It usually affects people aged 30 to 60. Some cases of early-onset disease are inherited and are called familial AD (FAD). The other is late-onset Alzheimer's disease. It is the most common form and occurs in those 65 and older

## DNA, Chromosomes, and Genes: The Body's Amazing Control Center



Click here for larger view

The nucleus of almost every human cell contains a vast chemical information database. This database carries all the instructions the cell needs to do its job. This database is **DNA**. DNA exists as two long, intertwined, thread-like strands packaged in units called **chromosomes**. Each cell has 46 chromosomes in 23 pairs. Chromosomes are made up of four chemicals, or bases, arranged in various sequence patterns. People inherit material in each chromosome from each parent.

Each chromosome has many thousands of segments, called **genes**. The sequence of bases in a gene tells the cell how to make specific proteins. Proteins determine the physical characteristics of living organisms. They also direct almost every aspect of the organism's construction, operation, and repair. Even slight alterations in a gene can produce an abnormal protein, which, in turn, can lead to cell malfunction, and eventually, to disease. Any rare change in a gene's DNA that causes a disease is called a **mutation**. Other more common (or frequent) changes in a gene's DNA don't automatically cause disease, but they can increase the chances that a person will develop a particular disease. When this happens, the changed gene is called a **genetic risk factor**.

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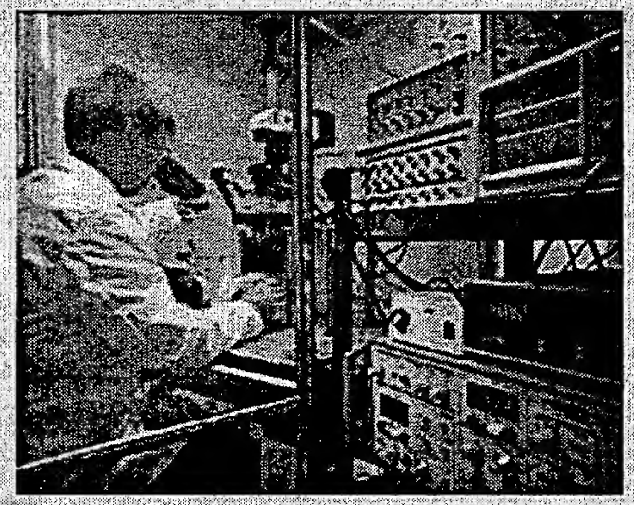
**Genes and Early-onset Alzheimer's Disease**

Over the past several decades, researchers working on AD realized that some cases, particularly of early-onset AD, ran in families. This led them to examine DNA samples from such families to see whether they had some genetic trait in common. Chromosomes 21, 14, and 1 became the focus of attention. The scientists found that some families have a mutation in selected genes on these chromosomes. On chromosome 21, the mutation causes an abnormal amyloid precursor protein (APP) to be produced. On chromosome 14, the mutation causes an abnormal protein called presenilin 1 to be produced. On chromosome 1, the mutation causes yet another abnormal protein to be produced. This protein, called presenilin 2, is very similar to presenilin 1. Even if only one of these genes inherited from a parent contains a mutation, the person will almost inevitably develop early-onset AD. This means that in these families, children have about a 50-50 chance of developing the disease if one of their parents has it.

Even though early-onset AD is very rare and mutations in these three genes do not play a role in the more common late-onset AD, these findings were crucial because they showed that genetics was indeed a factor in AD, and they helped to identify some key players in the AD disease process. Importantly, they showed that mutations in APP can cause AD, highlighting the key role of beta-amyloid in the disease. Many scientists believe that mutations in each of these genes cause an increased amount of the damaging beta-amyloid to be made in the brain.



The findings also laid the foundation for many other studies that have pushed back the boundaries of our knowledge and created new possibilities for future treatment. For example, in the last several years, a series of highly sophisticated experiments have shown that presenilin may actually be one of the **enzymes** (substances that cause or speed up a chemical reaction) that clips APP to form beta-amyloid (the protein fragment that is the main component of AD plaques). This discovery has helped clarify how presenilins might be involved in the early stages of AD. It has also given scientists crucial new targets for drug therapy and has spurred many new studies in the test tube, in animals, and even in people.

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**A Different Genetic Story in Late-onset Alzheimer's Disease**

While some scientists were focused on the role of chromosomes 21, 14, and 1 in early-onset AD, others were looking elsewhere to see if they could find genetic clues for the late-onset form. By 1992, these investigators had narrowed their search to a region of chromosome 19. At the same time, other colleagues were looking for proteins that bind to beta-amyloid. They were hoping to clarify some of the steps in the very early stages of the disease process. They found that one form of a protein called **apolipoprotein E** (ApoE) did bind quickly and tightly to beta-amyloid. They also found that the gene that produces ApoE was located in the same region of chromosome 19 pinpointed by the geneticists. This finding led them to suggest that one form of this gene was a risk factor for late-onset Alzheimer's disease.

Other studies since then have shown that the gene that produces ApoE comes in several forms, or alleles - e2, e3, and e4. The APOE e2 allele is relatively rare and may provide some protection against the disease. If AD does occur in a person with this allele, it develops later in life. APOE e3 is the most common allele. Researchers think it plays a neutral role in AD. APOE e4 occurs in about 40 percent of all AD patients who develop the disease in later life. It is not limited to people whose families have a history of AD, though. AD patients with no known family history of the disease are also more likely to have an APOE e4 allele than persons who do not have AD. Dozens of studies have confirmed that the APOE e4 allele increases the risk of developing AD. These studies have also helped to explain some of the variation in the age at which AD develops. However, inheriting an APOE e4 allele doesn't mean that a person will definitely develop AD. Some people with one or two APOE e4 alleles never get the disease and others who do develop AD do not have any APOE e4 alleles.

Although we still don't exactly know how APOE e4 increases AD risk, one theory is that when its protein product binds quickly and tightly to beta-amyloid, the normally soluble amyloid becomes insoluble. This may mean that it is more likely to be deposited in plaques.

While scientists are working to understand more fully the APOE gene and its role in AD, they have also identified regions on other chromosomes that might contain genetic risk factors. For example, in 2000, three teams of scientists, using three different strategies, published studies showing that chromosome 10 has a region that may contain several genes that might increase a person's risk of AD. Identifying these genes is one important step in the research process that will lead to new understanding about the ways in which changes in protein structures cause the disease process to begin and the sequence of events that occurs as the disease develops. Once they understand these processes, scientists can search for new ways to diagnose, treat, or even prevent AD.

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**Other Factors at Work in AD**
Even if genetics explains some of what might cause AD, it doesn't explain everything. So, researchers have looked at other possibilities that may reveal how the Alzheimer's disease process starts and develops.

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**Beta-amyloid**
We still don't know whether beta-amyloid plaques cause AD or whether they are a by-product of the disease process. We do know, however, that forming beta-amyloid from APP is a key process in AD. That's why finding out more about beta-amyloid is an important avenue of ongoing AD research. Investigators are studying:

- The nature of beta-amyloid
- Ways in which it is toxic to neurons
- Ways in which plaques form and are deposited
- Ways in which beta-amyloid and plaques might be reduced in the brain

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***Tau***
In the last few years, scientists have been giving an increasing amount of attention to tau, the other hallmark of Alzheimer's disease. This protein is commonly found in nerve cells throughout the brain. In AD, *tau* undergoes

changes that cause it to gather together abnormally in tangled filaments in neurons (for more on this, see the section **A Walking Tour Through the Brain**). In studying *tau* and what can go wrong, investigators have found that *tau* abnormalities are also central to other rare neurodegenerative diseases. These diseases, called *tau*opathies, include frontotemporal dementia, Pick's disease, supranuclear palsy, and corticobasal degeneration. They share a number of characteristics, but also each have distinct features that set them apart from each other and from AD. Characteristic signs and symptoms include changes in personality, social behavior, and language ability; difficulties in thinking and making decisions; poor coordination and balance; psychiatric symptoms; and dementia. Recent advances include the

discovery of mutations in the *tau* gene that cause one tauopathy called frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17). The development of several mouse models that produce *tau* tangles, will allow researchers to address the many questions that remain about these diseases. The development of a "double transgenic" mouse that has both *tau* tangles and beta-amyloid plaques will also lead to further insights about AD.

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**Cardiovascular Risk Factors**

Several recent studies in populations have found a possible link between factors related to cardiovascular disease and AD. One of these studies found that elevated levels of an amino acid called homocysteine, a risk factor for heart disease, are associated with an increased risk of developing AD. The relationship between AD and homocysteine is particularly interesting because blood levels of homocysteine can be reduced by increasing intake of folic acid and vitamins B6 and B12. In fact, in other studies, scientists have shown that folic acid may protect against nerve cell loss in brain regions affected by AD. Investigators have also found that the use of statins, the most common type of cholesterol-lowering drugs, is associated with a lower risk of developing AD.

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**Oxidative Damage from Free Radicals**

Another promising area of investigation relates to a longstanding theory of aging. This theory suggests that over time, damage from a kind of molecule called a free radical can build up in neurons, causing a loss in function. Free radicals can help cells in certain ways, such as fighting infection. However, too many can injure cells because they are very active and can readily change other nearby molecules, such as those in the neuron's cell membrane or in DNA. The resulting molecules can set off a chain reaction, releasing even more free radicals that can further damage neurons. This kind of damage is called oxidative damage. It may contribute to AD by upsetting the delicate machinery that controls the flow of substances in and out of the cell. The brain's unique characteristics, including its high rate of metabolism and its long-lived cells, may make it especially vulnerable to oxidative damage over the lifespan. Some epidemiological and laboratory studies suggest that anti-oxidants from dietary supplements or food may provide some protection against developing AD. Other studies suggest that low calorie diets may protect against the development of AD by slowing down metabolic rates.

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**Inflammation**
Another set of hints about the causes of AD points to inflammation in the brain. This process is part of the immune system and helps the body react to injury or disease. Fever, swelling, pain, or redness in other parts of the body are often signs of inflammation. Because cells and compounds that are known to be involved in inflammation are found in AD plaques, some researchers think it may play a role in AD.

They disagree, though, on whether inflammation is a good or a bad thing. Some think it is harmful - that it sets off a vicious cycle of events that ultimately causes neurons to die. Evidence from many studies supports this idea.

Other scientists believe that some aspects of the inflammatory process may be helpful - that they are part of a healing process in the brain. For example, certain inflammatory processes may play a role in combating the accumulation of plaques. Many studies are now underway to examine the different parts of the inflammatory process more fully and their effects on AD.

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**Brain Infarction**
We've all heard the sensible advice about ways to live a long and healthy life: eat right, exercise, don't smoke, wear a seat belt. All of these habits can help prevent heart attacks, stroke, and injuries. This advice may even have some relevance for AD as well. Results from one long-term study of aging and AD show that participants who had evidence of stroke in certain brain regions had more symptoms of dementia than could be explained by the number of plaques and tangles in their brain tissue. These findings suggest that damage to blood vessels in the brain may not be enough to cause AD, but that it could make AD clinical symptoms worse.

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